

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

DHB

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Studies of Adverse Effects of Marketed Drugs; Availability of Grants (Cooperative Agreements); Request for Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA), Center for Drug Evaluation and Research, is announcing the anticipated availability of funds for cooperative agreements to study adverse effects of drugs marketed in the United States and its territories. Subject to the availability of fiscal year 2002 funds, FDA anticipates that approximately \$900,000 will be available. FDA anticipates making up to three awards, each for up to \$300,000 per year (direct and indirects costs) for general databases that cover U.S. patients only, cover multiple States across the United States, had more than 1.5 million enrolled patients on December 31, 2000, and have the demonstrated ability to obtain paper copies of anonymized patient medical records.

Support for these agreements may be for up to 3 years subject to availability of future funds and satisfactory performance during the preceding year. The purpose of these agreements is to conduct drug safety analysis to the benefit of the public's health; respond expeditiously to urgent public safety concerns; provide a mechanism for collaborative pharmacoepidemiological research designed to test hypotheses, particularly those arising from suspected adverse reactions reported to FDA; and enable rapid access to U.S. population-based data sources to ensure public safety when necessary.

DATES: Submit applications by *[insert date 60 days after date of publication in the Federal Register]*.

ADDRESSES: Application kits are available from, and completed applications should be submitted to Rosemary T. Springer, Division of Contracts and Procurement Management (HFA-520), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7182.

Note: Applications hand-carried or commercially delivered should be addressed to 5630 Fishers Lane, rm. 2129, Rockville, MD 20857. Please DO NOT send applications to the Center for Scientific Review (CSR), National Institutes of Health (NIH). Applications mailed to CSR and not received by FDA in time for orderly processing will be returned to the applicant without consideration. Application forms can also be found at <http://www.nih.gov/grants/phs398/forms-toc.html>.

FOR FURTHER INFORMATION CONTACT:

Regarding the administrative and financial management aspects of this notice: Rosemary T. Springer (address above).

Regarding the programmatic aspects of this notice: David J. Graham, Office of Postmarketing Drug Risk Assessment (HFD-400), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-3238.

SUPPLEMENTARY INFORMATION: As stated later in this document, funding of the second and third years will be contingent upon: (1) Investigator's demonstrated success collaborating with FDA scientists, as well as with other investigators funded by this cooperative agreement program. Such demonstration may include suggestions for and design of a study, analysis of data sets, and publication of results among FDA and cooperative agreement investigators; and (2) the availability of Federal fiscal year appropriations.

It is determined that these cooperative agreements are exempt from the protection of human subjects requirements in accordance with 45 CFR part 46.

FDA's authority to fund research projects is set out in section 301 of the Public Health Service Act (42 U.S.C. 241). FDA's research program is described in the Catalog of Federal Domestic

Assistance, No. 93.103. Applications submitted under this program are not subject to the requirements of Executive Order 12372.

The Public Health Service (PHS) strongly encourages all grant recipients to provide a smoke-free workplace and to discourage the use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

FDA is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a national activity to reduce morbidity and mortality and to improve the quality of life. Applicants may obtain a hard copy of "Healthy People 2010" objectives, volumes I and II, Conference Edition (B0074) for \$22 per set, by writing to the Office of Disease Prevention and Health Promotion (ODPHP) Communication Support Center, P.O. Box 37366, Washington, DC 20013-7366. Each of the 28 chapters of "Healthy People 2010" is priced at \$2 per copy. Telephone orders can be placed with ODPHP on 301-468-5690. ODPHP also sells the complete Conference Edition in CD-ROM format (B0071) for \$5. This publication is also available on the Internet at www.health.gov/healthypeople under "Publications."

I. Background

New drugs are required to undergo extensive testing before marketing. Generally, if FDA determines that the manufacturer or sponsor of a new drug has submitted adequate data on the new drug's safety and effectiveness, the agency approves a new drug application (NDA) and that permits a manufacturer to market its product in the United States. Although the information provided before marketing is sufficient for approval, it is not adequate to anticipate all effects of a product once it comes into general use. This request for applications (RFA) is intended to encourage collaboration between FDA and researchers with pharmacoepidemiological databases representing U.S. patients to address postmarketing issues confronting the agency.

FDA is interested in the ability to measure and/or estimate incidence rates and test hypotheses based on signals of possible drug safety problems originating from adverse reaction reports received by FDA.

II. Program Research Goals

FDA shall fund up to three cooperative agreements whose databases represent, without overlap to each other or agency contracts, different U.S. patient populations.

The goal for these cooperative agreements is to collaborate with researchers who have pharmacoepidemiological databases, investigate suspected associations between specific drug exposures and specific adverse events, and estimate such risk. The specific objectives are to: (1) Provide immediate access to existing data sources with the capability of providing assessments of study feasibility, (2) respond to specific drug safety questions within a few weeks, and (3) provide a complete analysis to those questions deemed feasible within a few months.

Databases

For the purpose of this RFA, all \$300,000 awards will be to fund U.S. longitudinal databases that: (1) Cover U.S. patients only, (2) cover multiple States across the United States, (3) had more than 1.5 million enrolled patients on December 31, 2000, and (4) have the demonstrated ability to obtain paper copies of anonymized patient medical records.

These U.S. databases must be able to: (1) Provide exposure data on new molecular entities (those approved within the last 5 years in the United States), (2) perform feasibility studies of multiple drugs and/or multiple outcomes, (3) identify adverse drug events that occur infrequently (i.e., at rates lower than can be detected in clinical trials), (4) provide data and preliminary analysis within a very short timeframe (2 to 4 weeks depending on the problem), and (5) obtain paper copies of relevant anonymized patient medical records as required for completion and validation of studies under the cooperative agreement.

Database characteristics of interest include the ability to: (1) Estimate adverse event rates or relative risks for a specific event; (2) estimate the contribution of various risk factors associated with the occurrence of adverse events (e.g., age, sex, dose, coexisting disease, disease severity, and concomitant medication); (3) determine adverse event rates for generic entities as well as for classes of drugs; and (4) follow patients long term after an exposure to a suspect drug. Other

desirable, but not mandatory, characteristics include the ability to: (1) Obtain data from laboratory results, (2) link to State vital statistics, (3) link to cancer registries, and (4) determine inpatient exposure to drugs.

In addition, FDA is interested in databases capable of innovatively applying the objectives stated above to general populations.

The ideal data source would: (1) Capture all drug exposures linked longitudinally to each patient, regardless of health care delivery setting. Outcomes of interest could be either acute or chronic effects. All health provider encounters (i.e., medical records) would be captured whether in the ambulatory, emergency, chronic care, or acute care setting; (2) have the statistical power to identify rare (<1 event per 5,000 exposures) adverse events in the population of interest; (3) be automated with a computerized system available for linking each patient to all relevant medical care data including drug exposure data, coded medical outcomes, vital records, cancer registries, and birth defect registries; (4) have a low patient turnover, thereby permitting long-term longitudinal followup of most patients for delayed adverse effects (e.g., National Heart, Lung, and Blood Institute Framingham Heart Study); (5) address effects from chronically used drugs; and (6) address delayed effects resulting from drug use.

Submitted applications must include an indepth description of the database and provide descriptive and quantitative information on diagnoses or drug exposures in the population.

III. Reporting Requirements

Program progress reports will be required semiannually. The Progress Report Summary required for the Noncompeting Continuation Application is sufficient, if amended with the following information: (1) A list of all studies performed or in progress using cooperative agreement funds, categorized into those studies requested by FDA and all other studies; (2) copies of or a list of publications, abstracts, and presentations to professional organizations; (3) a list of the top 100 drug substance exposures for the previous year; and (4) a summary of any changes in the demographics or capabilities of the database over the last year. The Program Progress Reports

will be submitted as part of the Noncompeting Continuation Application (PHS-2590, OMB Control No. 0925-0001). You may exceed the two-page limit and should specify what you have done for the benefit of the public health. A final Progress Report will be required and must be submitted within 90 days after the expiration of the project period.

Financial Status Reports (SF-269, prescribed by OMB Circulars A-102 and A-110) will be required annually. These reports must be submitted within 90 days after the last day of the budget period of the cooperative agreement. Send the original and one copy of each document to the Grants Office at the address listed above. Failure to file the Annual Progress Report or the Financial Status Report (SF-269) in a timely fashion will be grounds for suspension or termination of the grant.

Program monitoring of the grantees will be conducted on an ongoing basis and written reports will be prepared by the Project Officer. The monitoring may be in the form of telephone conversations between the Project Officer and/or Grants Management Specialist and the Principal Investigator. Periodic site visits with appropriate officials of the grantee organization may also be conducted. The results of these reports will be recorded in the Official Grant File and may be available to the grantee upon request.

A final Program Progress Report and Financial Status Report (SF-269) must be submitted within 90 days after the expiration of the project period as noted on the Notice of Grant Award. Send the original and one copy to the Grants Management Officer at the address listed above.

Up to two representatives from each cooperative agreement may be required, if requested by the Project Officer, to travel to FDA up to twice a year for no more than 2 days at a time. These meetings will include, but are not limited to, presentation on study design and findings and discussions with FDA staff involved in the collaborative research. At least one FDA employee may visit the cooperative agreement site at least once a year for collaboration and information exchange.

IV. Mechanism of Support

A. Award Instrument

Support of this program will be in the form of cooperative agreements. All awards will be subject to all policies and requirements that govern the research grant programs of PHS, including the provisions of 42 CFR part 52, 45 CFR parts 74 and 92 and the PHS Grants Policy Statement.

B. Eligibility

These cooperative agreements are available to any domestic (U.S.) public or private nonprofit organization (including State and local governments) and any for-profit organization. For-profit organizations must exclude fees or profit from their requests for support. Organizations described in section 501(c)4 of the Internal Revenue Code of 1968 that engage in lobbying are not eligible to receive grant/cooperative agreement awards.

C. Length of Support

The first year will be competitive and future support for the second and third years will be noncompetitive. Future support will be contingent upon: (1) Investigator's demonstrated success collaborating with FDA scientists, as well as other investigators funded by this cooperative agreement program. Such demonstration may include suggestions for and design of a study, analysis of data sets, and publication of results from investigations performed by FDA and cooperative agreement investigators; and (2) the availability of Federal fiscal year appropriations.

D. Funding Plan

Up to three cooperative agreements may be funded for up to \$300,000 each per year with the intent that they will have large, general U.S. databases with the ability to address a variety of questions in the field of pharmacoepidemiology. These databases must: (1) Cover U.S. patients only, (2) cover multiple States across the United States, (3) have greater than 1.5 million enrolled patients on December 31, 2000, and (4) have demonstrated ability to obtain paper copies of

anonymized patient medical records. It is anticipated that these cooperative agreements will have a total of \$900,000 available per year.

These amounts are to include all direct and indirect costs. Federal funds for this program are limited, therefore, if two or more cooperative agreements are perceived as duplicative or very similar data sources with one another, FDA will support only the source with the best score. If any data source is perceived as duplicative or very similar to an existing FDA research contract, the contract will take precedence over the application. (FDA contracts include IMS Health, Inc., databases: National Prescription Audit Plus, National Disease and Therapeutic Index, Provider Prospective, Retail Prospective, Direct to Consumer-Integrated Promotional Services (Contract No. 223-01-5501)).

V. Delineation of Substantive Involvement

Inherent in the cooperative agreement award is substantive involvement by the awarding agency. Accordingly, FDA will have a substantive involvement in the programmatic activities of all projects funded under this RFA. Involvement may be modified to fit the unique characteristics of each application. Substantive involvement includes, but is not limited to, the following:

1. FDA will appoint Project Officers who will actively monitor the FDA supported program under each award and collaborate with award recipients.
2. FDA Project Officers will participate in the selection and approval of the drug and medical events to be studied as predicated by the needs of FDA and the public interest. The drug and medical events to be studied will be jointly agreed upon by the Principal Investigator and the FDA Project Officer.
3. FDA Project Officers and scientists will collaborate with awardees in study design and data analysis. Collaboration may include sharing of the analysis data set, interpretation of findings, review of manuscripts, design of protocols, and where appropriate, coauthorship of publications.

VI. Review Procedure and Criteria

A. Review Procedure

All applications submitted must be responsive to the RFA. Responsiveness is defined as adherence to the following review criteria. The requested budget should be within the limits of \$300,000 total cost (direct and indirect costs). Any application received that requests support in excess of the maximum amount allowable will be considered nonresponsive and returned to the applicant unreviewed. Also, this RFA is limited to databases that: (1) Cover U.S. patients only (2) cover multiple States across the United States, (3) had greater than 1.5 million enrolled patients as of December 31, 2000, and (4) have the demonstrated ability to obtain paper copies of anonymized patient medical records. Those applications failing to meet any of the above criteria will be classified as nonresponsive, will not be considered for funding under this RFA, and will be returned to the applicant unreviewed.

Responsive applications will undergo dual peer review. A review panel of experts, comprised primarily of non-Federal scientists, in the fields of epidemiology, statistics, and database management will review and evaluate each application based on its scientific merit. Responsive applications will also be subject to a second level review by a National Advisory Council for concurrence with the recommendations made by the first level reviewers, and the final funding decisions will be made by the Commissioner of Food and Drugs (the Commissioner) or the Commissioner's designee.

B. Review Criteria

Applicants are strongly encouraged to contact FDA to resolve any questions regarding criteria or administrative procedures prior to the submission of their application. See the **FOR FURTHER INFORMATION CONTACT** section of this document for contact information.

Applications will be reviewed according to the following criteria, with each criteria being of equal weight within each major category, unless otherwise specified. All applications will be scored with a maximum of 500 points allowable.

The size and characteristics of the general, longitudinal database should include the following:

1. Database Characteristics (255 points)

a. Structure (70 points). Raw data from multiple State sites is stored in a central database repository at one site. All analysis data sets are efficiently derived from this central database. (70 points)

There is no central database where raw data from all State sites is collected and stored. However, the same data elements defined in the same way are stored in multiple databases corresponding to the multiple State sites. The data structure at each of these multiple sites allows easy integration across sites to create a unified analysis data set. (30 points)

b. Size (70 points). Applicants should list number of patients enrolled in their database as of December 31, 2000.

- 3 million covered lives (70 points)
- 2.5 to 3 million covered lives (40 points)
- 2 to 2.5 million covered lives (30 points)
- 1.5 to 2 million covered lives (10 points)

c. Duration (55 points). The calendar time-period for which detailed patient longitudinal data are available and linked for routine, day-to-day analysis from at least 80 percent of the multiple State sites.

- 5 years of data online (0 points)
- 5 years of data online (25 points)
- 6 points for each additional year beyond 5 years of online data to a possible total of 55 points

d. General database features (60 points). A maximum of five points and a minimum of zero points will be awarded for each of the following criterion:

1. Provide a detailed process description and timeline of the process for creating a cohort based on drug exposure or clinical diagnosis. Include a list of data fields available for determining drug exposure and clinical diagnoses or procedures. In addition, include an estimate of the number and type of personnel and percentage of personnel commitment necessary for achieving this task.
2. Provide a detailed description of how patient demographic, health provider encounters, and drug exposure data are linked for the purposes of analysis. Include information on the specific variable(s) used to link the data together, and a description of information pulled from each file.
3. Provide age, ethnicity, gender distribution, and total number of participants where appropriate for the populations listed below as categories (a) through (e). All questions should be answered using the 2000 calendar year as a reference. (Please note that this list is only a sample for evaluation purposes, and that the specific target populations of future interest to FDA and the public may not be explicitly defined here.) Include the definitions used to obtain the cohorts listed. Please also provide, wherever possible, publications or studies regarding any of the following special populations that describe studies of adverse drug reactions conducted in your database:
 - (a) Children (those under 21 years of age as of December 31, 2000),
 - (b) Women between the ages of 18 and 50 as of December 31, 2000,
 - (c) Persons aged 65 and above as of December 31, 2000,
 - (d) Deliveries as of December 31, 2000, and
 - (e) Persons diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) as of December 31, 2000 (include definition of HIV/AIDS).
4. Provide a detailed description of the patient enrollment and turnover rates for the past 5 years. Include data specifying the numbers of new patients and departing patients for each year, as well as the average length of enrollment.
5. Provide a description of the drug and disease classification systems used in the database. Include the generally accepted name of the system, revision currently used, and a reference to the organization that maintains the classification standard.

6. Provide a detailed process description and timeline for retrieving and reviewing 100 medical records for validity of a diagnosis. Include an estimate of the number and type of personnel and percentage of personnel commitment necessary for achieving this task.

7. Provide a published reference or report referencing the occasion in which the database was used to link to a cancer registry and to State vital statistics for an investigation. If no report or reference is available, please describe in detail how these linkages could be accomplished using the database. Include a list of variables available for linking and a detailed description of the linking algorithm.

8. Provide three reports or references in which a drug-drug interaction was the focus of the investigation. If no reports or references are available, provide a detailed description of how such a study could be conducted using the database. Include an explanation of how the cohort for the study would be created and followed and how drug interactions would be defined.

9. Provide a detailed process description and timeline between a patient event (office visit, hospitalization, etc.) and the availability of data from that event for analysis.

10. Provide a list of the top 50 drug substances of exposure contained in the database. Include the drug and number of exposures as of December 31, 2000.

11. Provide the name and description of the software package used to calculate person-time at risk and time of event occurrence in the database. If the software package is not commercially available (e.g., SAS, SPSS, S+, Stata), include the algorithm used by the software.

12. Provide a description of the applicant organization's ability to generate anonymized data sets that can be provided to authorized FDA personnel for further analysis or data pooling purposes. Include a description and timeline of the clearance or other procedures necessary for this process to occur. If this is not possible due to database or other constraints, provide a detailed explanation of why data sets cannot be exported for research purposes.

2. New Molecular Entity (NME) Identification (200 points)

In table 1 of this document, 40 recently approved NME's are listed. Applicants should respond with the number of unique patients in their system with at least 1 outpatient prescription for each of the 40 drug products listed in table 1. For each drug, points will be awarded by the review panel according to the following schedule:

- 25,000 exposed patients (5 points)
- 20,001 to 25,000 exposed patients (4 points)
- 15,001 to 20,000 exposed patients (3 point)
- 10,001 to 15,000 exposed patients (2 points)
- 5,001 to 10,000 exposed patients (1 point)
- 5,000 or fewer exposed patients (0 points).

FDA recognizes that no database will receive full points for every drug requested, or necessarily have each of the drugs listed in the table in their formulary. FDA is interested in the ability of each database to address potential safety issues related to recently approved drugs, now and in the future. NME's eligible for scoring with the previously described criteria are shown in table 1 below:

TABLE 1.—NEW MOLECULAR ENTITIES

Brand Name	Year Approved
Aciphex	1999
Actonel	1998
Actos	1999
Amerge	1998
Avandia	1999
Avelox	1999
Celebrex	1998
Celexa	1998
Comtan	1999
Detrol	1998
Evista	1997
Evoxac	2000
Flomax	1997
Gabitril	1997
Lotronex	2000
Maxalt	1998
Meridia	1997
Micardis	1998
Mirapex	1997
Mobic	2000
Pletal	1999
Posicor	1997
Prandin	1997
Protonix	2000
Provigil	1998
Raxar	1997

TABLE 1.—NEW MOLECULAR ENTITIES—Continued

Brand Name	Year Approved
Relenza	1999
Rezulin	1997
Singulair	1998
Sonata	1999
Tamiflu	1999
Tasmar	1998
Tikosyn	1999
Trovan	1997
Viagra	1998
Vioxx	1999
Xenical	1999
Ziagen	1998
Zomig	1997
Zyvox	2000

3. Personnel (20 points)

Personnel should have the following qualifications:

a. Scientific (15 points).—Extensive research experience, training, and competence. Special consideration will be given to teams with knowledge and previous experience in drug epidemiology. Applicants with strong acute and chronic disease epidemiology backgrounds and a demonstrated ability to draw on consultative expertise (particularly in the areas of postmarketing surveillance and epidemiology) are encouraged to apply. (If consultants are used, letters of intent or other contractual agreements, including beginning and end dates, shall be included in the application to fulfill this requirement.) Demonstrated ability to initiate, conduct, complete, and publish epidemiology studies in a timely manner.

b. Support (5 points).—Project management and information systems expertise with previous experience in the organization and manipulation of large data sets and specific experience in databases under agreement.

4. Data Sharing (15 points)

To provide study data sets (free of patient identifiers and in a format usable to the agency) to Project Officers of FDA for analysis and with other cooperative agreement holders in studies that would require data pooling.

5. Budget (10 points)

Reasonableness of the proposed budget. Special consideration will be given to methodology which is cost effective (e.g., well-structured medical records and/or records linkage) if otherwise scientifically acceptable.

VII. Submission Requirements

The original and two copies of the completed Grant Application Form PHS 398 (revised 4/98 OMB Control No. 0925-0001) or the original and two copies of Form 5161 for State and local governments (Revised 7/00, OMB Control No. 0348-0042), with sufficient copies of the appendix for each application should be delivered to Rosemary T. Springer (address above). State and local governments may choose to use the PHS 398 application in lieu of the PHS 5161. No supplemental material will be accepted after the closing date. The outside of the mailing package should be labeled "Response to RFA-FDA-CDER-02-1". The application receipt date is *[insert date 60 days after date of publication in the Federal Register]*.

VIII. Method of Application

A. Submission Instructions

Applications will be accepted during normal working hours, 8 a.m. to 4:30 p.m., Monday through Friday, on or before *[insert date 60 days after date of publication in the Federal Register]*.

Applications will be considered received on time if sent or mailed on or before the receipt date as evidenced by the legible U.S. Postal Service dated postmark or a legible date receipt from a commercial carrier, unless they arrive too late for orderly processing. Private metered postmarks shall not be acceptable as proof of timely mailing. Applications not received on time will not be considered for review and will be returned to the applicant.

Note: Applicants should note that the U.S. Postal Service does not uniformly provide dated postmarks. Before relying on this method, applicants should check with their local post office.

Do not send applications to CSR, NIH. Any application that is sent to NIH, that is then forwarded to FDA and received after the applicable due date, will be deemed unresponsive and returned to the applicant. Instructions for completing the application forms can be found on the NIH home page on the Internet (address <http://www.nih.gov/grants/funding/phs398/phs398.html>; the application forms can be found at http://www.nih.gov/grants/funding/phs398/forms__toc.html). However, as noted above, applications are not to be mailed to NIH. Applicants are advised that FDA does not adhere to the page limitations or type size and line spacing requirements imposed by NIH on its applications. Applications must be submitted via mail delivery as stated above. FDA is unable to receive applications via the Internet.

B. Format of Application

Applications must be submitted on Grant Application Form PHS 398 (revised 4/98). All "General Instructions" and "Specific Instructions" in the application kit should be followed with the exception of the receipt dates and the mailing label addresses. Do not send applications to CSR, NIH. Applications from State and local governments may be submitted on Form PHS 5161 (revised 6/99) or PHS 398 (revised 4/98). The face page of the application must reflect the request for applications number RFA-FDA-CDER-02-1. This information collection is approved under OMB control number 0925-0001.


C. Legend

Data included in the application, if restricted with the legend specified below, may be entitled to confidential treatment as trade secret or confidential commercial information within the meaning of the Freedom of Information Act (FOIA) (5 U.S.C. 552(b)(4)) and FDA's implementing regulations (21 CFR 20.61).

Unless disclosure is required by FOIA as amended (5 U.S.C. 552) as determined by the freedom of information officials of the Department of Health and Human Services or by a court, data contained in the portions of the application that have been specifically identified by page

number, paragraph, etc., by the applicant as containing confidential commercial information or other information that is exempt from public disclosure will not be used or disclosed except for evaluation purposes.

Dated: 5/29/01
March 29, 2001.



William K. Hubbard,
Senior Associate Commissioner for Policy, Planning, and Legislation.

[FR Doc. 01-????? Filed ??-??-01; 8:45 am]

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